REMARKS

In an interview between Examiner Chong and Larry Frank, on December 21, 2006, Examiner Chong indicated that the Office Action mailed on June 27, 2006 was a non-final Office Action. This is in agreement with page 2 of the pending Office Action, but contrary to what is specified on page 8 of the Office Action which the Examiner indicated is a typograpical error. As such, we were instructed that we were not required to file a notice of appeal with our response to the Office Action. The Examiner stated that he would send an interview summary to that effect.

Claims 19-27, 29-35, and 54-68 are pending in the subject application. Claims 20, 24-25, and 31-35 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claims 19-27 and 29-35 are rejected as obvious under 35 U.S.C. § 103

Claims 20, 24-25, and 31-35 have been amended by deleting the term "solution" and, except in claim 33, replacing it with the term "pharmaceutical preparation." New claims 54-68 depend from claims 20, 22-27, and 29-35 and are directed to pharmaceutical preparations wherein the ester of 5-aminolevulinic acid is ALA hexylester. Applicants submit that the present amendment adds no new matter. Support for the amendments is found at, inter alia, page 3, lines 13-14, page 4, lines 19-23, and page 5, lines 17-23.

Upon entry of the present amendment, Claims 19-27, 29-35, and 54-68 will be pending and under examination. Applicants respectfully request entry of this amendment.

Claim Rejections Under 35 U.S.C. § 112

It is believed that deletion of the term "solution" in Claims 20, 24-25, and 31-35 and, except in Claim 33, replacement of that term with "pharmaceutical preparation" overcomes the rejection of the claims under 35 U.S.C. § 112, second paragraph because all claim terms in the claims as amended have sufficient antecedent basis. Applicants respectfully request that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

The pending claims, directed to pharmaceutical preparations comprising an ester of 5-aminolevulinic acid at a concentration of less than 1% by weight, stand rejected as obvious over Gierskcky et al. (United States Patent No. 6,034,267) ("Gierskcky"). The Examiner maintains that Gierskcky states that suitable ALA ester concentrations generally are 1-50%. The Examiner concedes that Gierskcky does not specifically disclose the use of ALA esters at

concentrations of less than 1%, as claimed in this application. However, according to the Examiner, it is well established that merely selecting proportions and ranges is not patentable absent a showing of criticality. The Examiner maintains that the articles by Peng et al. ("Peng"), Lang et al. ("Lang"), and Marti et al. ("Marti") would have motivated the person of ordinary skill to modify the explicitly disclosed concentration ranges of Gierskcky to arrive at the instantly claimed concentration ranges.

For reasons detailed below, Applicants respectfully submit that the currently pending claims are not rendered obvious by the references cited by the Examiner.

First, it should be noted, as Applicants pointed out in their June 27, 2005 Amendment, that the articles by Lang and Marti ***are not prior art*** to the instant application and therefore cannot provide a basis for finding the instant claims obvious. The instant application was filed on April 22, 1999 and claims priority to French Application No. 98/05425, filed on April 22, 1998 (Applicant's claim to priority was made on October 20, 2000 and acknowledged on March 27, 2002.). Marti et al. was published in July 1999 and Lange et al. in May 1999 (Lange would be considered published in May of 1999 because that is when it became available in libraries (*see* date-stamped copy in Amendment dated June 27, 2005)), both after the instant application's United States filing date.

Second, the presently claimed invention is based on the discovery that ALA esters may be successfully utilized for treatment of tissue pathologies at concentrations below 1%, ***thereby reducing any toxicity associated with the use of higher concentrations of ALA esters***. None of the references cited by the Examiner either teach or suggest such a result.

Regarding the Peng reference, Applicants maintain that Peng in fact teaches away from the instant invention by disclosing the use of ALA esters at a concentration of about 20%, over twenty times higher than the highest ALA ester concentration encompassed by the instant claims. In view of this teaching, the person of ordinary skill in the art would not have had any expectation that compositions having much lower ALA-ester concentrations, such as those presently claimed, would have been therapeutically or diagnostically useful.

Similarly, Gierskcky fails to explicitly disclose the use of of ALA-esters at concentrations below 1%, such as those presently claimed. Applicants maintain that the person of ordinary skill in the art would not have had a reasonable expectation of success in using a concentration below the lowest concentration generally disclosed by Gierskcky. Rather, such a person would have expected that, in general, the higher the concentration of ALA-ester, the more porphyrins would be produced *in vivo* and the more effective the treatment would be, so long as absorption by normal tissue and other side effects are

minimized. It would, therefore, be counterintuitive to expect that a composition with a lower ALA-ester concentration would be as or more effective than one with a higher concentration. Thus, the person of ordinary skill in the art generally would not have expected ALA-ester concentrations of less than 1% to be as, or more, effective than concentrations above 1%.

Further, as set forth in detail in the Amendment filed on June 27, 2005, Applicants have demonstrated the criticality of ALA ester concentrations below 1%. As the Examiner acknowledges in the most recent Office Action, a showing of criticality overcomes an obviousness rejection. In this regard, the Examiner's attention is directed to the Declaration under 37 C.F.R. § 1.132 of Georges Wagnières ("Wagnières Declaration") filed on January 26, 2004, which demonstrates that ALA- octyl and -hexyl esters produce a maximum PpIX fluorescence at concentrations well below 1% (*See also* June 27, 2005 Amendment, p.11, and modified Exhibits). Applicants maintain that such data supports criticality because it is desirable to use as little material as possible to achieve the maximum effect, in order to introduce as little of a foreign substance as possible into the treated patient, among other reasons (for example, treatment cost, minimization of any side effects).

The Office Action dismisses the results obtained with the ALA octyl ester because the octyl ester precipitated at the higher concentrations tested. Applicants maintain that the available evidence indicates that the octyl ester most effectively induces PpIX fluorescence at concentrations well below 1% (*See* June 27, 2005 Amendment, p.11, and modified Exhibits). This data cannot be overcome by mere speculation that different results would be obtained if precipitation did not occur. Absent data showing that higher PpIX fluorescence can be obtained at higher ALA octyl ester concentrations, it should be concluded that criticality of ALA octyl ester concentrations below 1% has been demonstrated.

The butyl ALA ester also induces maximum PpIX fluorescence at a concentration well below 1% (*See* June 27, 2005 Amendment, p.11, and modified Exhibits), however, the Office Action contends that criticality is not shown for the butyl ALA ester because it also induces fluorescence at a concentration above 1%. Applicants point out that the peak fluorescence is at a concentration below 1%, thus criticality is thereby demonstrated.

For similar reasons, Applicants maintain that criticality has been shown for ALA-ethylester (*See also* June 27, 2005 Amendment, p.11, and modified Exhibits). Although peak fluorescence is not observed, but is predicted to occur at a concentration of about 1%, Applicants contend that it is surprising and unexpected that ALA-ethylester can effectively induce significant fluorescence at concentrations well below 1%.

Further, according to the Wagnières Declaration, compositions having the claim recited ALA-hexylester concentration of less than 1% yield surprising and unexpected results when used in models for photodynamic therapy and diagnosis. As noted, in two different cell lines (J82 and T24), ALA-hexylester induced PpIX production that peaked unexpectedly at an ALA-hexylester concentration of about 0.01% or less. *See* Exhibit C of the Wagnières Declaration (*See also* June 27, 2005 Amendment, p.11, and modified Exhibits). Similar surprising results were obtained using a pig bladder model. *See* Exhibit E of the Wagnières Declaration (*See also* June 27, 2005 Amendment, p.11, and modified Exhibits). Finally, it was suprisingly found that a 0.2% ALA-hexylester pharmaceutical preparation, induced greater PpIX fluorescence than a comparable preparation containing 3% ALA. *See* Exhibit H of the Wagnières Declaration, (*See also* June 27, 2005 Amendment, p.11, and modified Exhibits).

These results are unexpected in light of the cited Gierskcky reference because they indicate that relatively high fluorescence is obtained at concentrations well below the lower limit of the generally disclosed ranges disclosed by Gierskcky. This is counterintuitive and thus unexpected because ALA-hexylester induces porphyrin synthesis, and the person of ordinary skill in the art would expect the quantity of porphyrins to increase with increasing ALA-hexylester concentration, whereas the opposite is observed above the ALA-hexylester concentration that yields peak fluorescence. Peak fluorescence occurred at or below about 0.01% ALA-hexylester, which is 1/100th of the disclosed range minimum.

In sum, the data of the Wagnières Declaration demonstrate the criticality of ALA-hexylester concentrations below 1% because such concentrations have the surprising property that they induce substantially greater amounts of fluorescence than ALA-hexylester concentrations within the range disclosed by the asserted Gierskcky prior art reference. Applicants respectfully request allowance of new claims 54-68 in view of the demonstrated criticality of the recited ALA-hexylester concentrations and the Examiner's acknowledgment thereof.

Applicants maintain that the obviousness rejection of the Examiner is based on two publications that are not prior art (Lang and Marti), a third reference that teaches away and provides no reasonable expectation of success (Peng), and a fourth reference (Gierskcky) that provides no reasonable expectation of success. In sum, the asserted prior art does not render the claims *prima facie* obvious. Further, the Applicants' data as set forth in the Wagnières Declaration demonstrates the criticality of ALA ester concentrations of less than 1% generally and for ALA hexylester specifically, thereby overcoming any potential *prima facie* obviousness case. Applicants therefore respectfully request withdrawal of the obviousness rejection for the reasons set forth above.

CONCLUSION

All objections and rejections having been addressed, it is respectfully submitted that the present application is now in condition for allowance, which action is respectfully requested. The Examiner is invited to contact Applicants' representative to discuss any issue that would expedite allowance of the subject application.

Respectfully submitted,

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